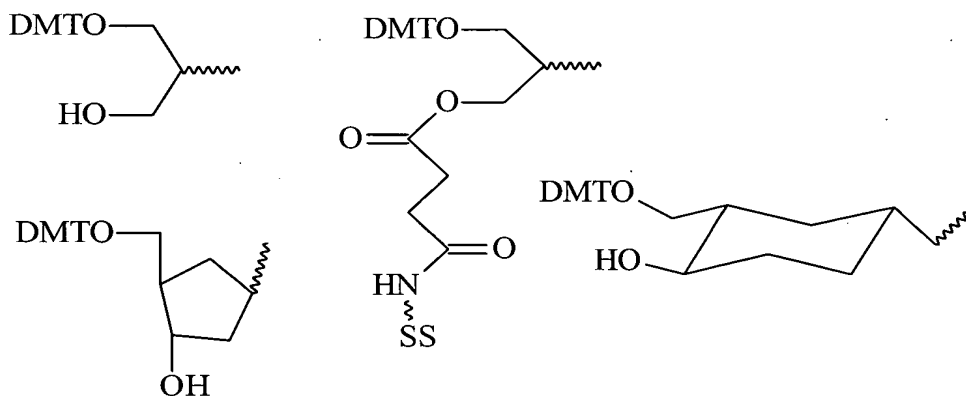
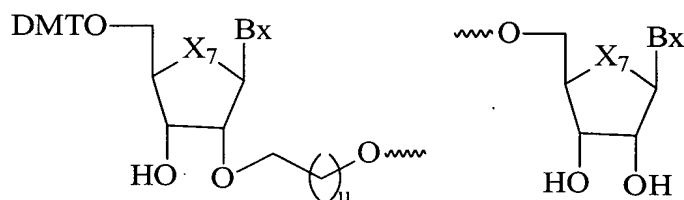


Claims 1-7. (Canceled)

9. (Previously Presented) The compound of claim 112 wherein said X₄ is the side chain of glutamic acid.

$$\text{DMTO}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\left(\text{CH}_2\right)_u-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{N}\left(\text{CH}_2\right)_z-\text{OH}$$


SS is a solid support;
X₇ is O or CH₂;

Bx is a nucleobase, C₄-C₁₄ heterocyclyl or hydrogen;
z is an integer from 1 to 50; and
u is an integer from 2 to 5.

11. (Previously Presented) The compound of claim 112 wherein said R₁ is dimethoxytrityl.

Claims 12-31 (Canceled).

32. (Previously Presented) The method of claim 104 wherein W₁ has the formula -O-(CH₂)_n-NH-, wherein n is from 1 to about 10.

33. (Original) The method of claim 32 wherein n is 6.

34. (Canceled)

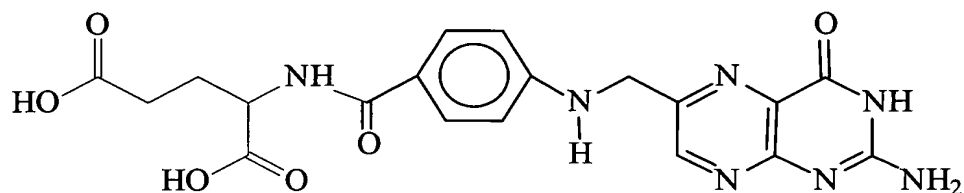
35. (Previously Presented) The method of claim 104 wherein R₁ is dimethoxytrityl, A has the formula -O-(CH₂)_n-NH- where n is 6, m is 2, R₄ is t-butoxy, R₅ is trifluoroacetyl, R₆ is -C(=O)-CH(CH₃)₂, and R₃₀ is FMOX.

Claims 36-39 (Canceled).

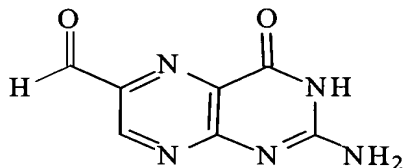
40. (Previously Presented) The method of claim 105 wherein R₁ is dimethoxytrityl, W₁ has the formula -O-(CH₂)_n-NH- where n is 6, m is 2, R₄ is t-butoxy, R₅ is trifluoroacetyl, R₆ is -C(=O)-CH(CH₃)₂, and R₃₀ is FMOX.

41. (Canceled)

42. (Currently Amended) The method of claim 106 26 wherein said compound IX is prepared by reacting folic acid:



with a reagent effective to form pterin aldehyde:



and

protecting the amino group of said pterin aldehyde.

Claims 43-62 (Canceled).

63 (Previously Presented). The compound of claim 115 wherein m is 2.

64. (Original) The compound of claim 63 wherein W_1 is
-O-(CH₂)₆-NH-.

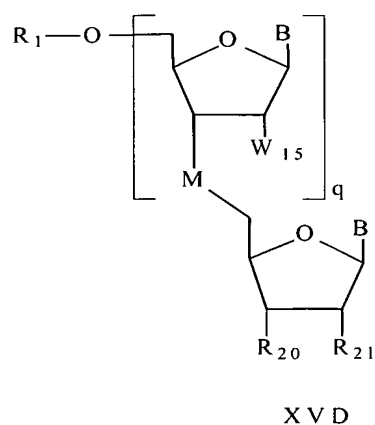
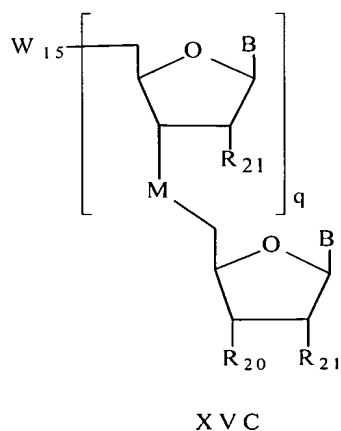
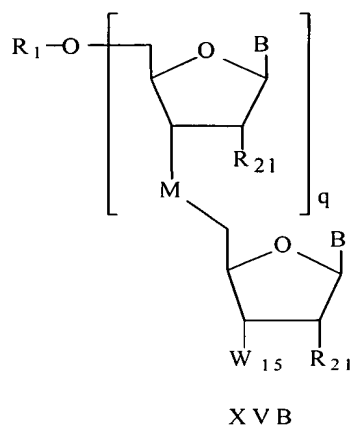
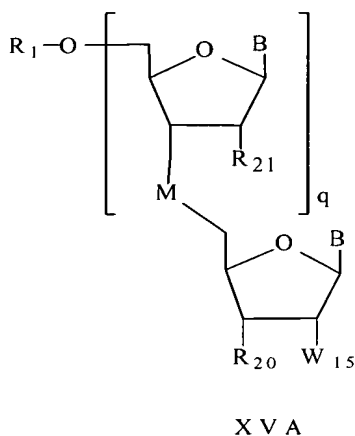
65. (Previously Presented) The compound of claim 64 wherein R₄ is t-butoxy.

66 (Original). The compound of claim 65 wherein R_1 is dimethoxytrityl, R_5 is trifluoroacetyl, and R_6 is $-C(=O)-CH(CH_3)_2$.

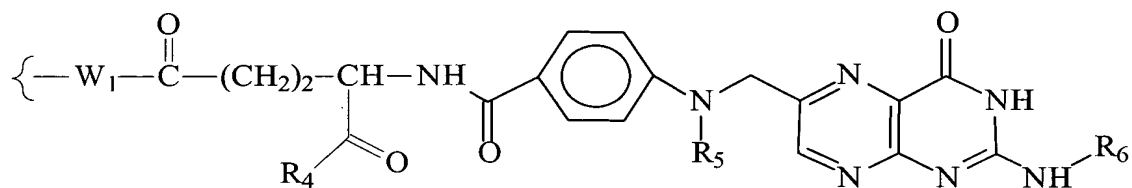
67 (Original). The compound of claim 66 wherein q is 0.

Claims 68-71 (Canceled).

72 (Original). A composition comprising a compound of claim 63, said composition being substantially free of a compound of formula XVA, XVB, XVC or XVD:



wherein W_{15} has the formula:



Claims 73-78 (Canceled).

79 (Previously Presented). The compound of claim 116 wherein m is 2.

80 (Original). The compound of claim 79 wherein W_1 is $-O-(CH_2)_n-NH-$ wherein n is from 1 to about 10.

81 (Original). The compound of claim 80 wherein n is 6.

Claims 82-87 (Canceled).

88. (Previously Presented) The compound of claim 117 wherein m is 2.

89. (Original) The compound of claim 88 wherein W_1 is $-O-(CH_2)_n-NH-$ wherein n is from 1 to about 10.

90. (Original) The compound of claim 89 wherein n is 6.

Claims 91 and 92 (Canceled).

DOCKET NO.: ISIS-4803
Application No.: 09/973,981
Office Action Dated: February 4, 2004

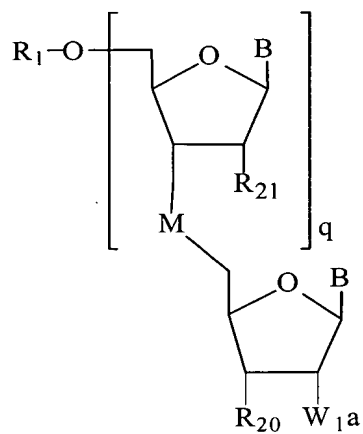
PATENT

93 (Previously Presented). The compound of claim 112 wherein said R₄ is a hydroxyl group protected with C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl or C₂-C₂₀ alkynyl.

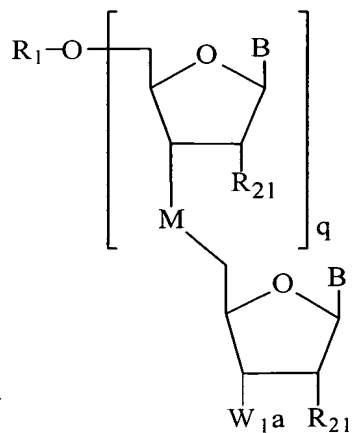
Claims 94-103 (Canceled).

104 (Previously Presented) A synthetic method comprising the steps of:

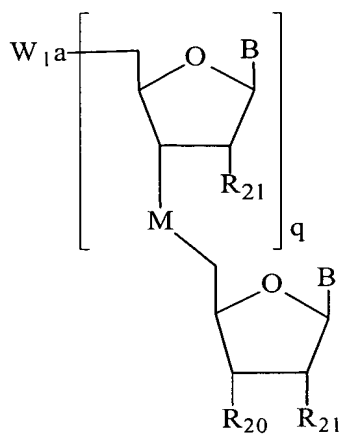
(a) providing a compound of formula IA, IB, IC or ID:



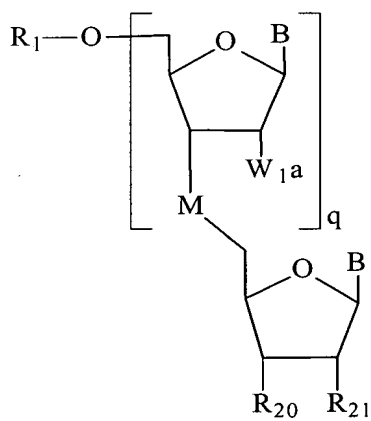
IA



IB



IC



ID

wherein:

W_{1a} is W_{1b} -H, OH, NH_2 or SH, where W_{1b} is a linking group;

R_1 is H or a hydroxyl protecting group;

B is a nucleobase;

each R_{21} is H, OH, F, or a group of formula $Z-R_{22}-(R_{23})_v$;

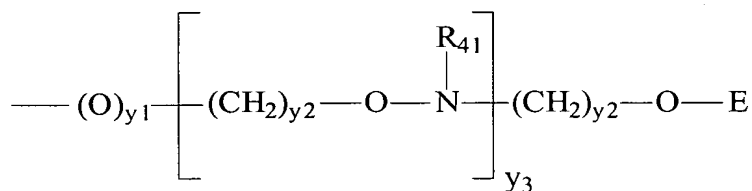
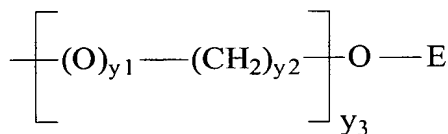
Z is O, S, NH, or $N-R_{22}-(R_{23})_v$

R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether;

v is from 0 to about 10;

or R_{21} has one of the formulas:



wherein:

y₁ is 0 or 1;

y₂ is 0 to 10;

y₃ is 1 to 10;

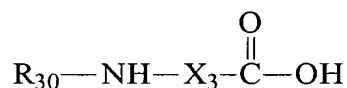
E is N(R₄₁)(R₄₂) or N=C(R₄₁)(R₄₂);

each R₄₁ and each R₄₂ is independently H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₄₁ and R₄₂ taken together form a nitrogen protecting group; or R₄₁ and R₄₂ taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

q is from zero to about 50, provided that when said compound has formula ID, q is at least 1;

M is an optionally protected internucleoside linkage;

(b) reacting said compound of formula I with a compound of formula II:

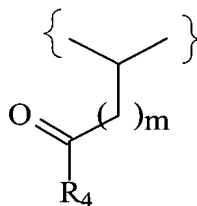


II

wherein:

R₃₀ is an amino protecting group;

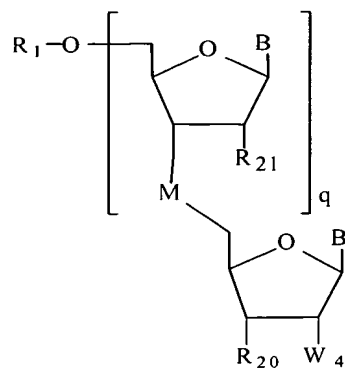
X₃ is a group of formula XII:



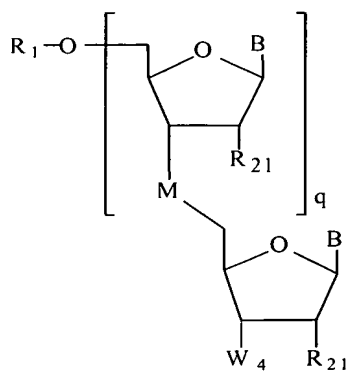
XII

wherein m is 1 or 2;

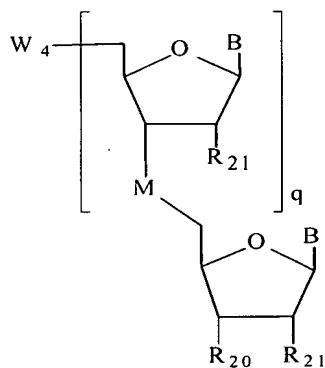
R_4 is a hydroxyl group, or a protected hydroxyl group;
 to form a compound of formula IVA, IVB, IVC, or IVD:



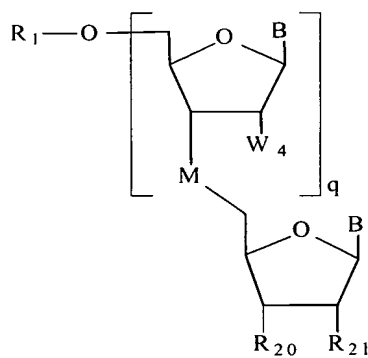
IV A



IV B



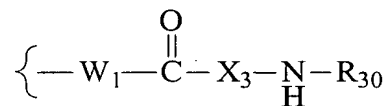
IV C



IV D

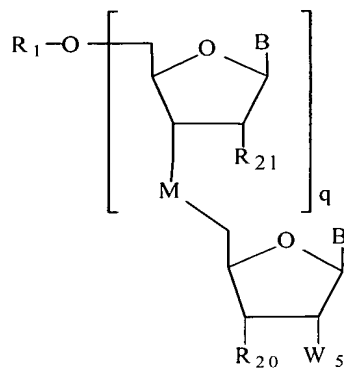
wherein:

W_4 has the formula:

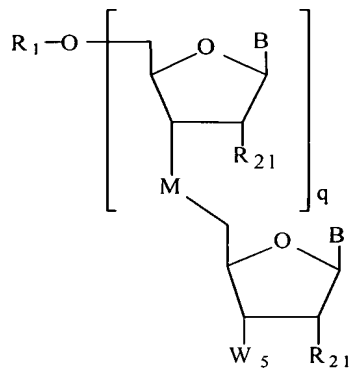


where W_1 is a linking group, O, NH, or S; and

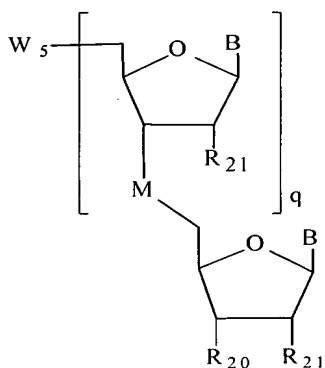
treating said compound of formula IVA, IVB, IVC or IVD with a deprotecting reagent to form a compound of formula VA, VB, VC or VD:



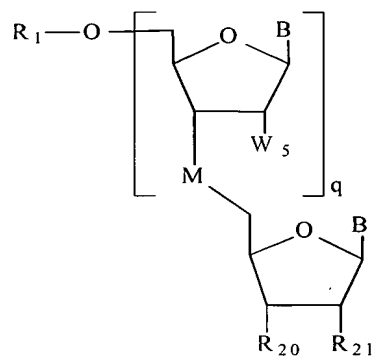
VA



VB

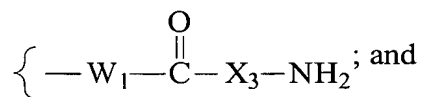


VC



VD

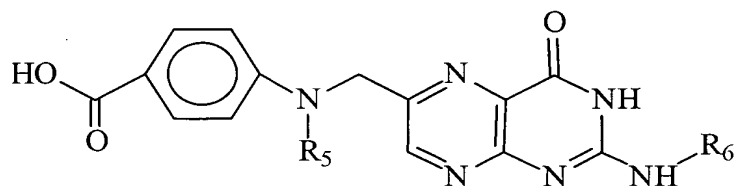
wherein W_5 has the formula:



(c) condensing said compound of Formula V with a compound of Formula VI:

DOCKET NO.: ISIS-4803
Application No.: 09/973,981
Office Action Dated: February 4, 2004

PATENT



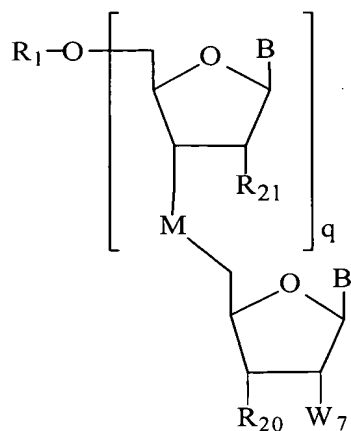
VI

wherein:

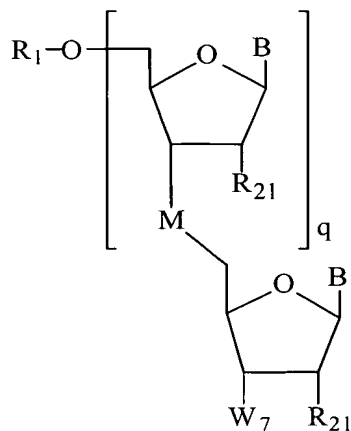
R₅ is H or an amino protecting group;

R₆ is H or an amino protecting group;

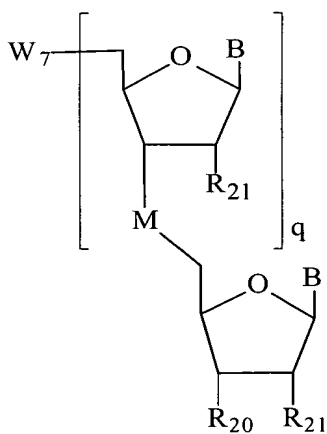
to form a compound of Formula VIIA, VIIB, VIIC, or VIID:



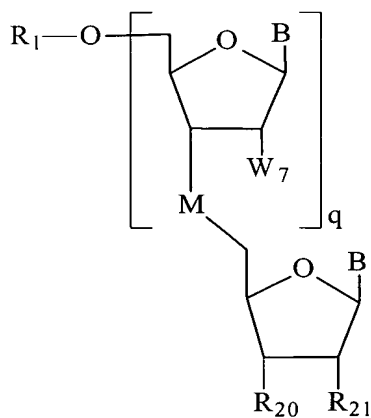
VIIA



VIIB



VIIC

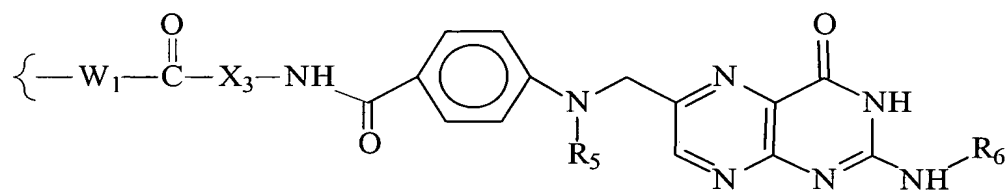


VIID

DOCKET NO.: ISIS-4803
Application No.: 09/973,981
Office Action Dated: February 4, 2004

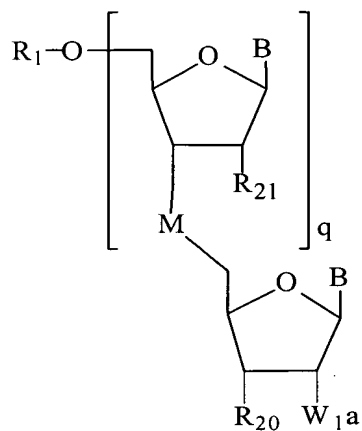
PATENT

wherein W_7 has the Formula:

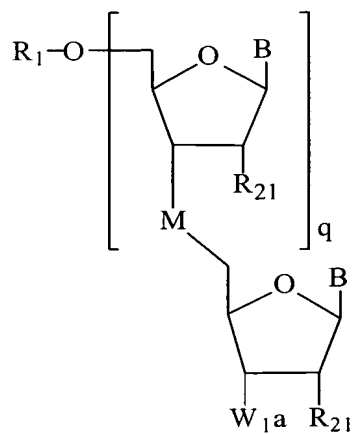


105. (Previously Presented) A synthetic method comprising the steps of:

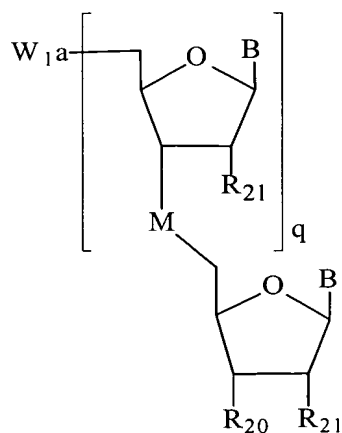
(a) providing a compound of formula IA, IB, IC or ID:



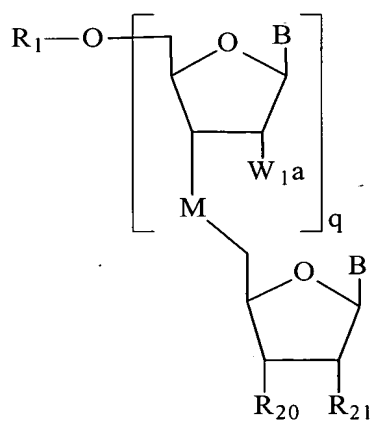
IA



IB



IC



ID

wherein:

W_{1a} is W_{1b} -H, OH, NH_2 or SH, where W_{1b} is a linking group;

R_1 is H or a hydroxyl protecting group;

B is a nucleobase;

each R_{21} is H, OH, F, or a group of formula $Z-R_{22}-(R_{23})_v$;

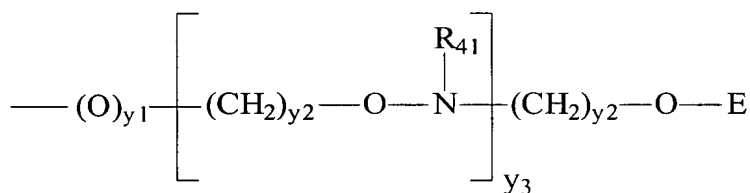
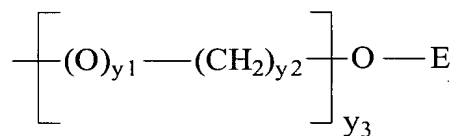
Z is O, S, NH, or $N-R_{22}-(R_{23})_v$

R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether;

v is from 0 to about 10;

or R_{21} has one of the formulas:



wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

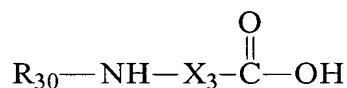
E is N(R₄₁)(R₄₂) or N=C(R₄₁)(R₄₂);

each R₄₁ and each R₄₂ is independently H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₄₁ and R₄₂ taken together form a nitrogen protecting group; or R₄₁ and R₄₂ taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

q is from zero to about 50, provided that when said compound has formula ID, q is at least 1;

M is an optionally protected internucleoside linkage;

(b) reacting said compound of formula I with a compound of formula II:

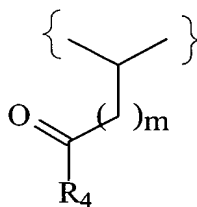


II

wherein:

R₃₀ is an amino protecting group;

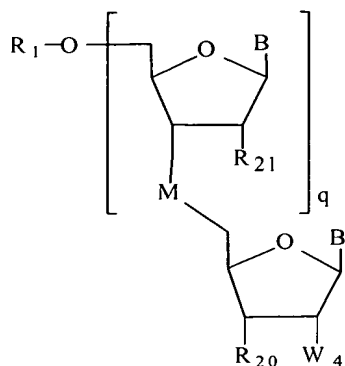
X₃ is a group of formula XII:



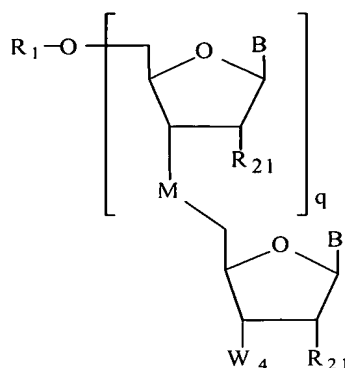
XII

wherein m is 1 or 2;

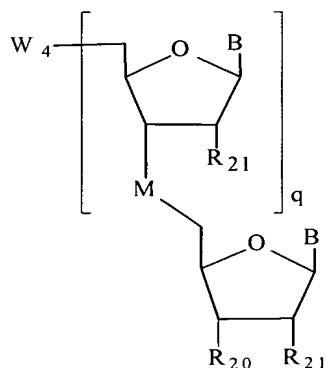
R_4 is a hydroxyl group, or a protected hydroxyl group;
 to form a compound of formula IVA, IVB, IVC, or IVD:



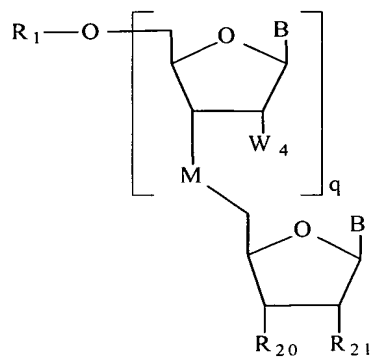
IV A



IV B



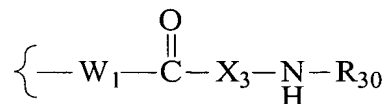
IV C



IV D

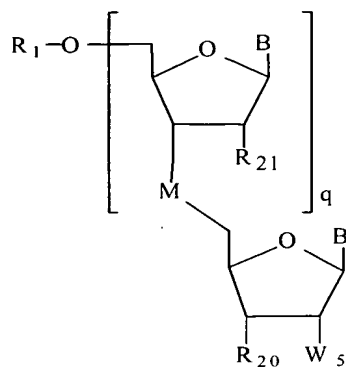
wherein:

W_4 has the formula:

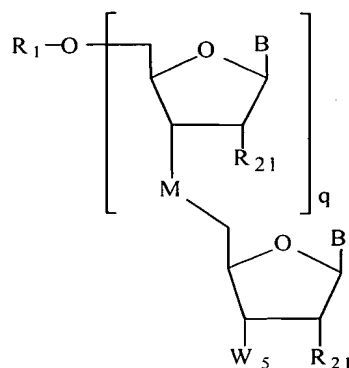


where W_1 is a linking group, O, NH, or S; and

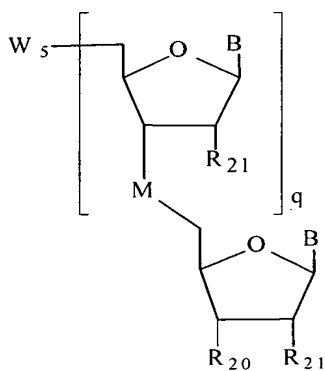
treating said compound of formula IVA, IVB, IVC or IVD with a deprotecting reagent to form a compound of formula VA, VB, VC or VD:



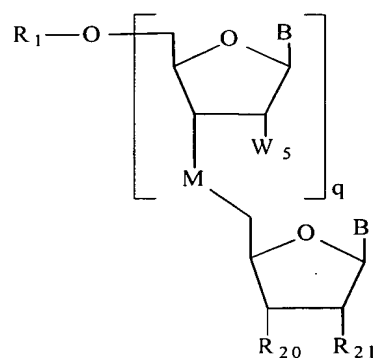
VA



VB

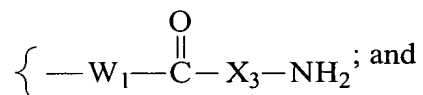


VC

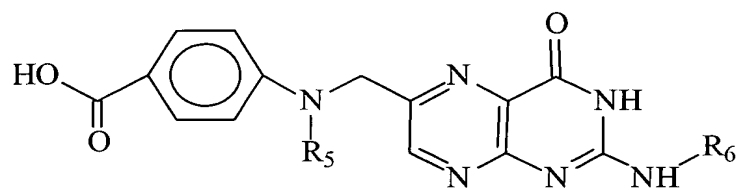


VD

wherein W_5 has the formula:



(c) condensing said compound of Formula V with a compound of Formula VI:



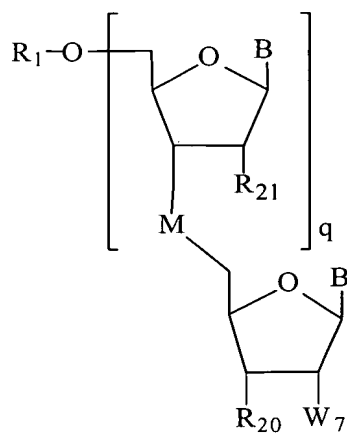
VI

wherein:

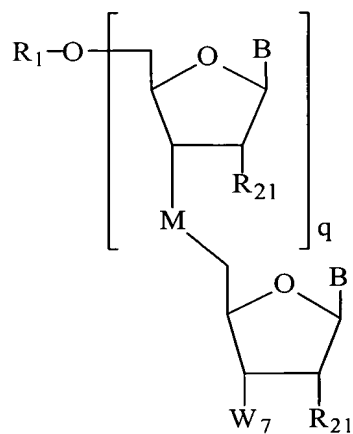
R₅ is H or an amino protecting group;

R₆ is H or an amino protecting group;

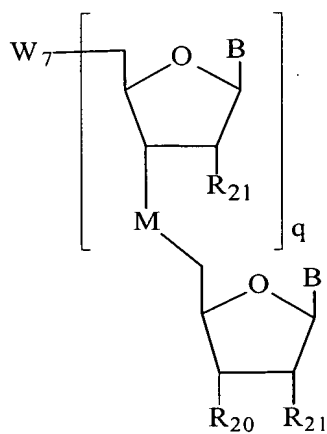
to form a compound of Formula VIIA, VIIB, VIIC, or VIID:



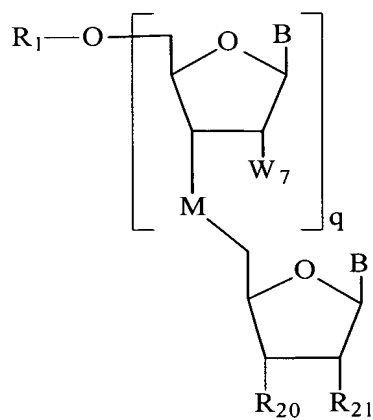
VIIA



VIIB

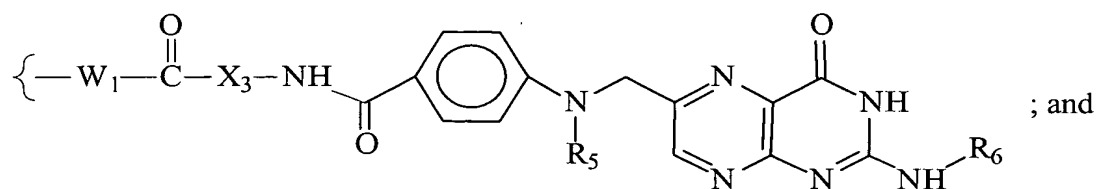


VIIC

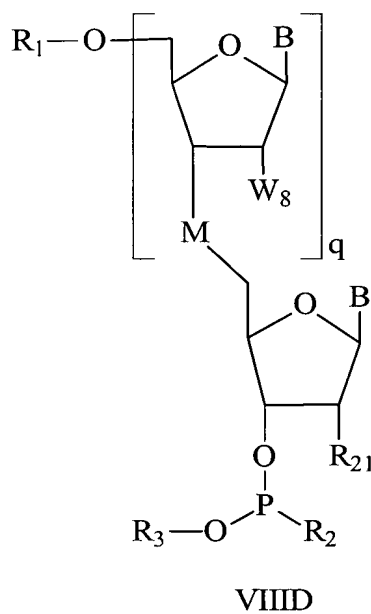
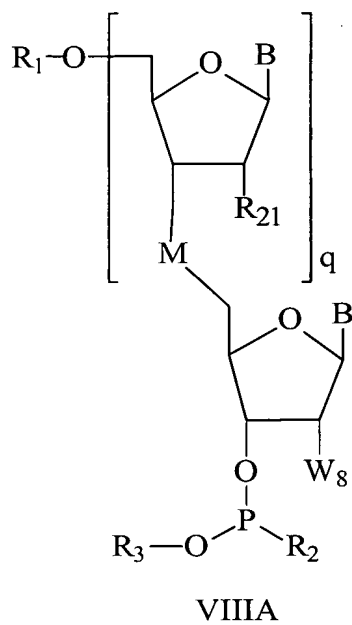


VIID

wherein W_7 has the Formula:



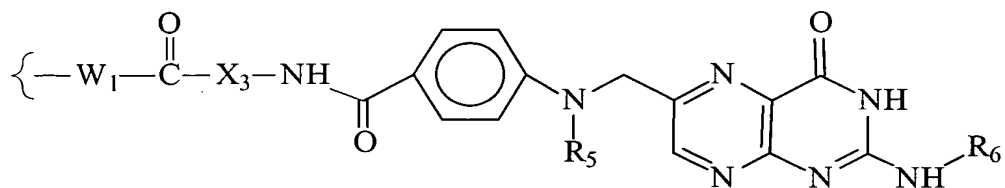
- (d) contacting said compound of Formula VIIA or VIID with a phosphitylating reagent to form a compound of Formula VIIIA or VIID:



wherein W_7 has the Formula:

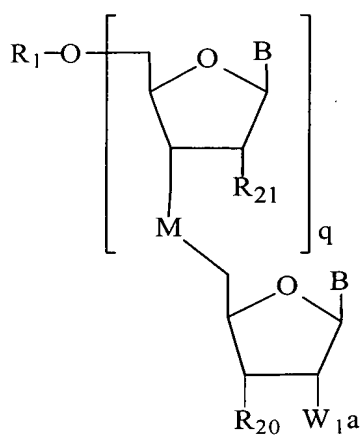
DOCKET NO.: ISIS-4803
Application No.: 09/973,981
Office Action Dated: February 4, 2004

PATENT

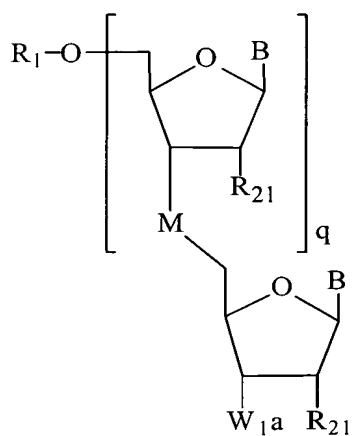


106 (Previously Presented). A synthetic method comprising the steps of:

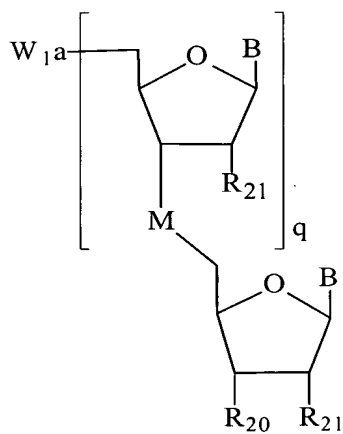
(a) providing a compound of formula IA, IB, IC or ID:



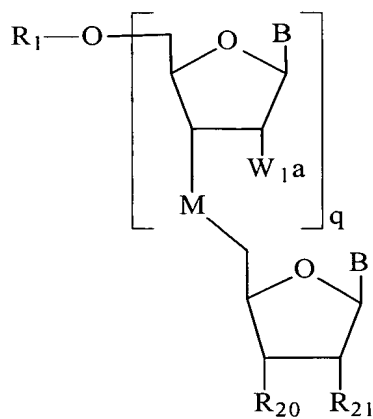
IA



IB



IC



ID

wherein:

W_{1a} is W_{1b} -H, OH, NH_2 or SH, where W_{1b} is a linking group;

R_1 is H or a hydroxyl protecting group;

B is a nucleobase;

each R_{21} is H, OH, F, or a group of formula $Z-R_{22}-(R_{23})_v$;

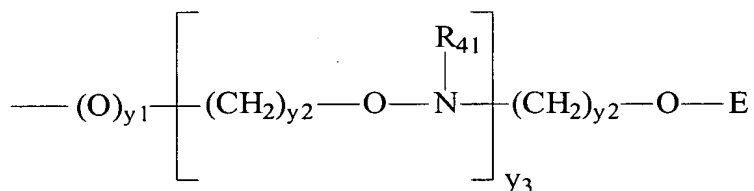
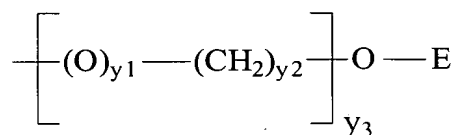
Z is O, S, NH, or $N-R_{22}-(R_{23})_v$

R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether;

v is from 0 to about 10;

or R_{21} has one of the formulas:



wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

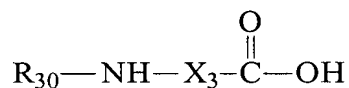
E is N(R₄₁)(R₄₂) or N=C(R₄₁)(R₄₂);

each R₄₁ and each R₄₂ is independently H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₄₁ and R₄₂ taken together form a nitrogen protecting group; or R₄₁ and R₄₂ taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

q is from zero to about 50, provided that when said compound has formula ID, q is at least 1;

M is an optionally protected internucleoside linkage;

(b) reacting said compound of formula I with a compound of formula II:

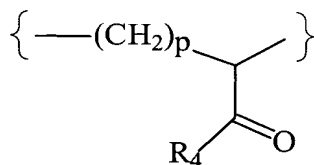


II

wherein:

R₃₀ is an amino protecting group;

X₃ is a group of formula XI:

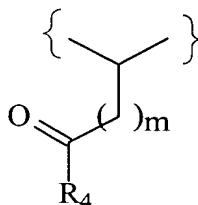


XI

wherein:

p is 1 or 2;

R₄ is a hydroxyl group, or a protected hydroxy group;
or X₃ is a group of formula XII:

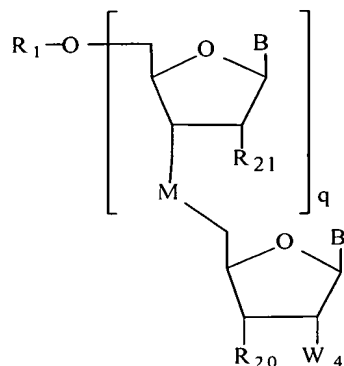


wherein m is 1 or 2;

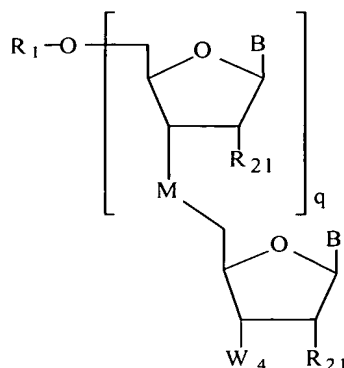
Z₁ is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

R₄ is a hydroxyl group, or a protected hydroxyl group;

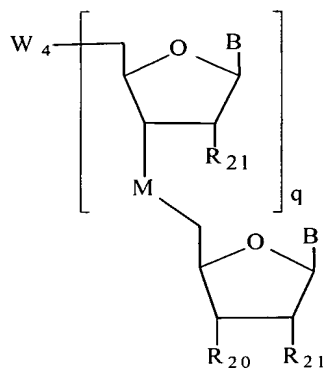
p is 1 or 2; to form a compound of formula IVA, IVB, IVC, or IVD:



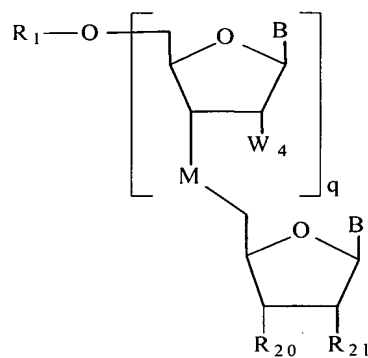
IV A



IV B



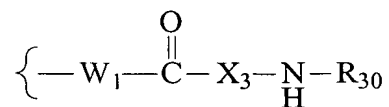
IV C



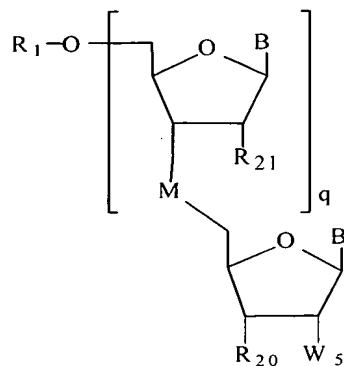
IV D

wherein:

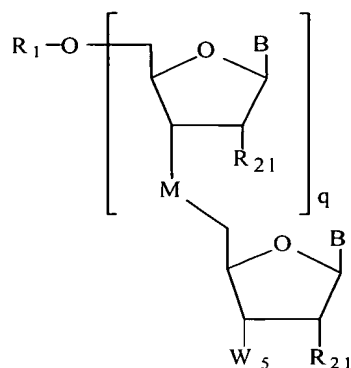
W₄ has the formula:



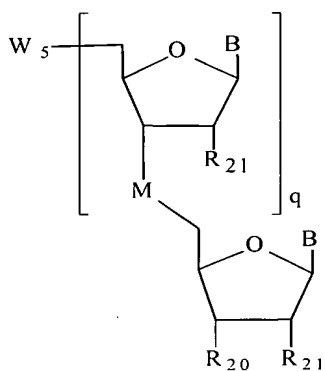
where W₁ is a linking group, O, NH, or S; and
 treating said compound of formula IVA, IVB, IVC or IVD with a deprotecting reagent to form a
 compound of formula VA, VB, VC or VD:



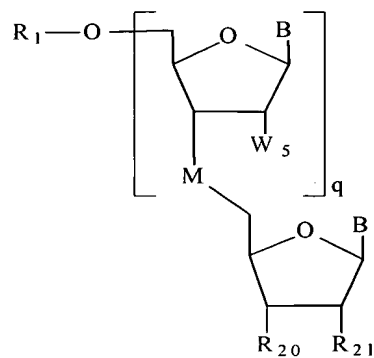
V A



V B

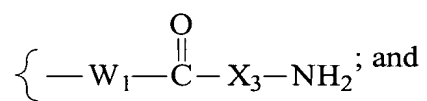


V C

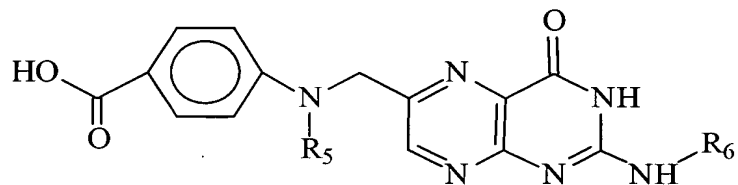


V D

wherein W_5 has the formula:



(c) condensing said compound of Formula V with a compound of Formula VI:



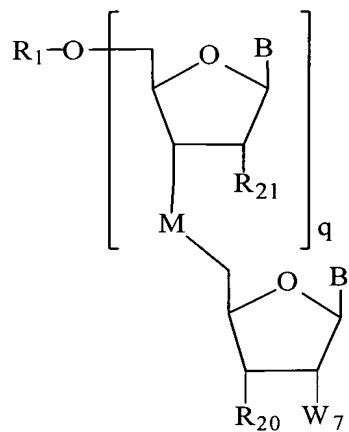
VI

wherein:

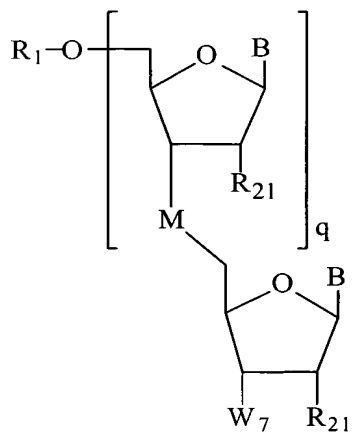
R₅ is H or an amino protecting group;

R₆ is H or an amino protecting group;

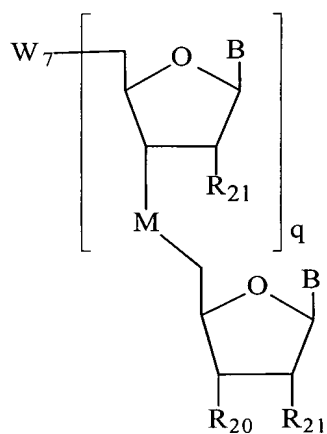
to form a compound of Formula VIIA, VIIB, VIIC, or VIID:



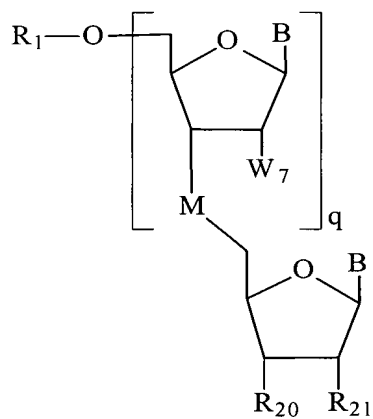
VIIA



VIIB

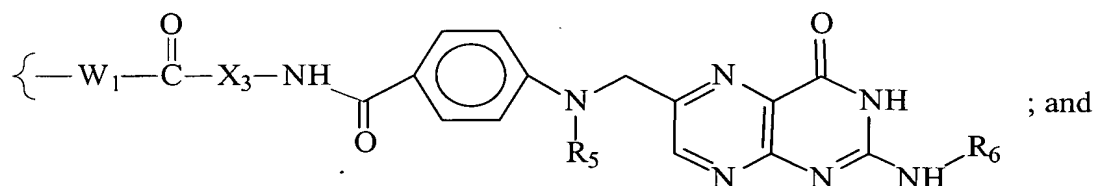


VIIC

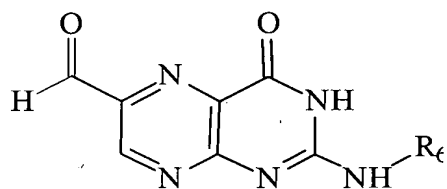


VIID

wherein W_7 has the Formula:

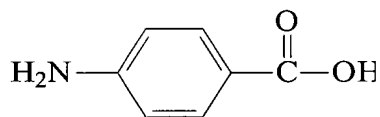


wherein said compound of formula VI is prepared by the steps of reacting a compound of formula IX:



IX

with a compound of formula X:

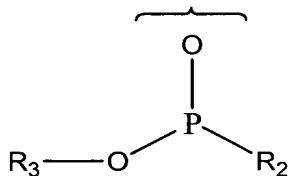


X

and treating the product of said reaction with a protecting group reagent to form said compound of formula VI.

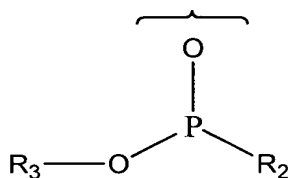
Claims 107-109 (Canceled)

110 (Previously Presented). The compound of claim 112 wherein said R_{20} is a group of formula:



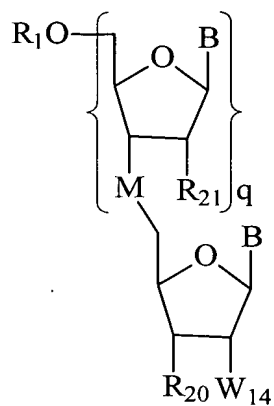
wherein R_2 is diisopropylamino and R_3 is β -cyanoethyl.

111 (Previously Presented). The compound of claim 67 wherein R_{20} is a group of formula:

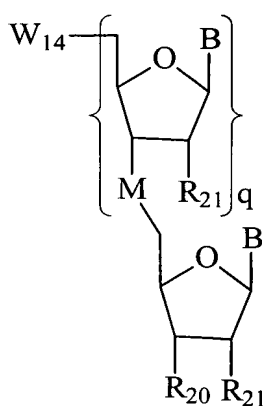


where R_3 is β -cyanoethyl, and R_2 is diisopropylamino.

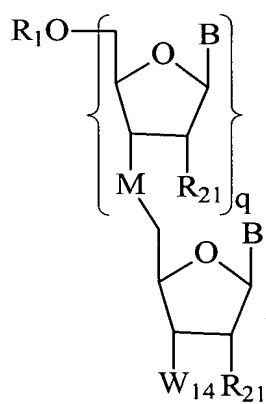
112 (Previously Presented). A compound having formula XVIA, XVIB, XVIC or XVID:



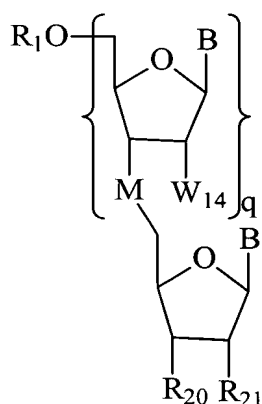
XVIA



XVIC



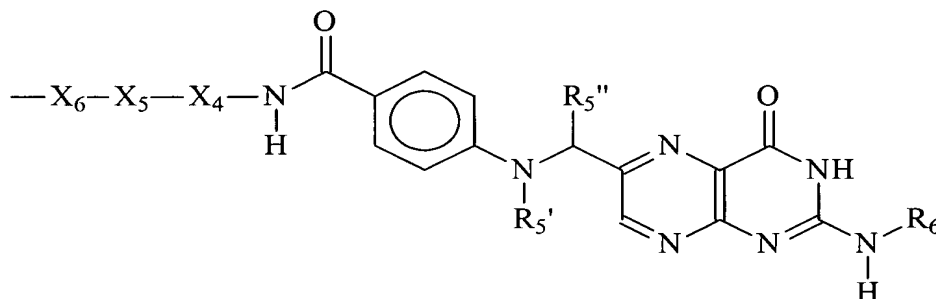
XVIB



XVID

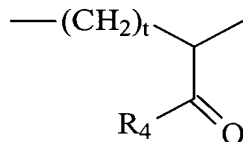
wherein:

W_{14} has the formula



wherein:

X_4 is $-\text{CH}(X_4)$ or a group of formula:



X_4 is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

X_5 is $-\text{N}(X_6)\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{NHC}(\text{O})-$, $-\text{OC}(\text{O})\text{NH}-$, $-\text{C}(\text{S})\text{NH}-$, $-\text{SC}(\text{S})\text{NH}-$, $-\text{SC}(\text{O})\text{NH}-$, $-\text{OC}(\text{S})\text{NH}-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})(\text{CH}_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6 and X_6' is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl, C_6 - C_{14} aralkyl, C_3 - C_{14} cycloalkyl, C_5 - C_{14} fused cycloalkyl, C_4 - C_{14} heterocycle, C_4 - C_{14} heterocyclylalkyl, C_4 - C_{14} heteroaryl and C_4 - C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups,

and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen and X_6 is not a bond;

R_1 is hydrogen or a hydroxyl protecting group;

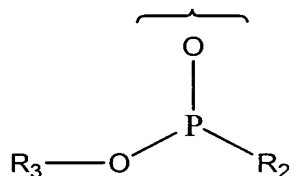
R_4 is a hydroxyl group or a protected hydroxyl group;

each R_5 and R_{40} is, independently, hydrogen, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl or an amino-protecting group

$R_{5'}$ is hydrogen, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl, C_6 - C_{14} aralkyl, C_3 - C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

R_6 is hydrogen or an amino protecting group;

R_{20} is hydroxyl or a group of formula:



R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

R_3 is a phosphorus protecting group;

R_{21} is hydrogen, hydroxyl, fluoro or a group of formula $Z-R_{22}-(R_{23})_v$;

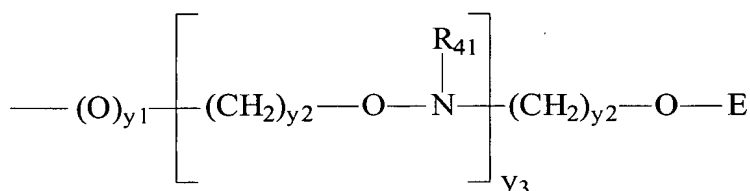
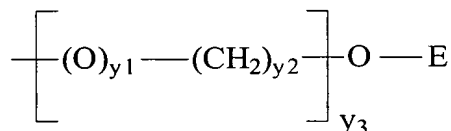
Z is O, S, NH or $N-R_{22}-(R_{23})_v$;

R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino,

hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether;

or R₂₁ has one of the formulas:



wherein:

y₁ is 0 or 1;

each y₂ is, independently, 0 to 10;

y₃ is 1 to 10;

E is N(R₄₁)(R₄₂) or N=C(R₄₁)(R₄₂);

each R₄₁ and each R₄₂ is independently H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₄₁ and R₄₂ taken together form a nitrogen protecting group; or R₄₁ and R₄₂ taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

B is a nucleobase;

M is an optionally protected internucleoside linkage;

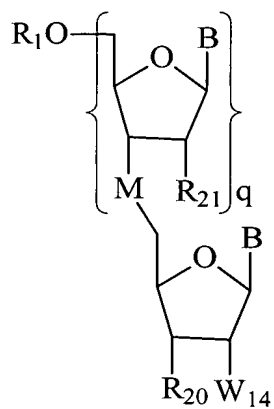
q is 0 to about 50; and

DOCKET NO.: ISIS-4803
Application No.: 09/973,981
Office Action Dated: February 4, 2004

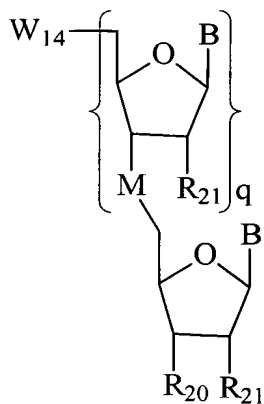
PATENT

v is from zero to about 10;
provided that when said compound has formula XVID, q is at least 1.

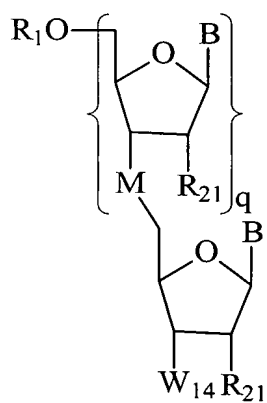
113 (Previously Presented). A compound having formula XVIA, XVIB, XVIC or XVID:



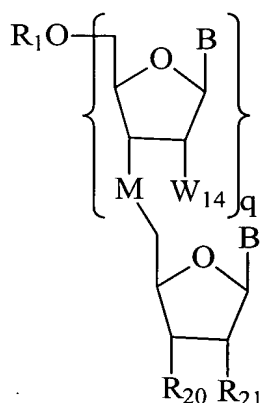
XVIA



XVIC



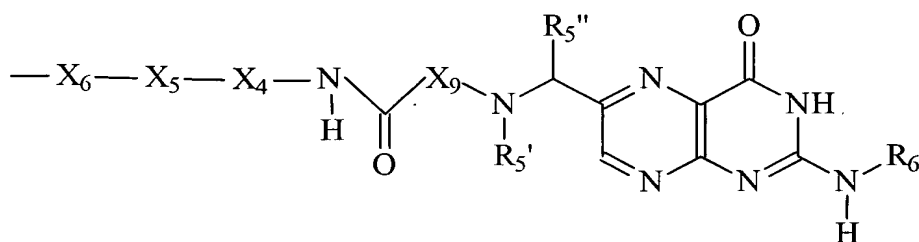
XVIB



XVID

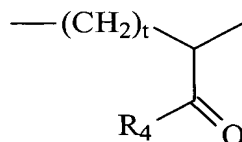
wherein:

W₁₄ has the formula:



wherein:

X₄ is $-CH(X_4)$ or a group of formula:



X₄ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

X₅ is $-N(X_6)C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$, $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$, $-C(O)(CH_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X₆, X_{6'} and X₉ is, independently, a bond, hydrogen or a hydrocarbyl group selected from C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₂₀ alkynyl, C₆-C₁₄ aryl, C₆-C₁₄ aralkyl, C₃-C₁₄ cycloalkyl,

C₅-C₁₄ fused cycloalkyl, C₄-C₁₄ heterocycle, C₄-C₁₄ heterocyclylalkyl, C₄-C₁₄ heteroaryl and C₄-C₁₄ heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that each X₆ and X₉ is not hydrogen and X₆ is not a bond;

R₁ is hydrogen or a hydroxyl protecting group;

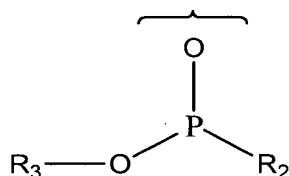
R₄ is a hydroxyl group or a protected hydroxyl group;

each R₅ and R₄₀ is, independently, hydrogen, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₂₀ alkynyl, C₆-C₁₄ aryl or an amino-protecting group

R_{5a} is hydrogen, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₂₀ alkynyl, C₆-C₁₄ aryl, C₆-C₁₄ aralkyl, C₃-C₁₄ cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

R₆ is hydrogen or an amino protecting group;

R₂₀ is hydroxyl or a group of formula:



R₂ is -N(R₇)₂, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

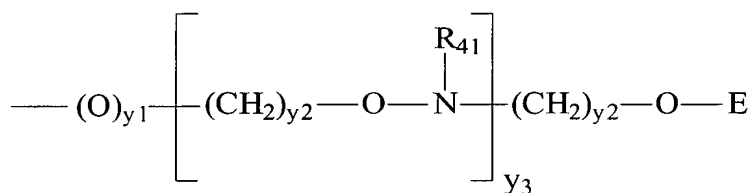
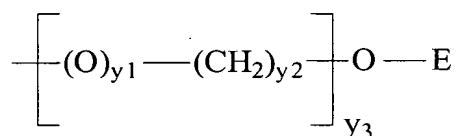
R₂₁ is hydrogen, hydroxyl, fluoro or a group of formula Z-R₂₂-(R₂₃)_v;

Z is O, S, NH or N-R₂₂-(R₂₃)_v;

R₂₂ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, or C₂-C₂₀ alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether;

or R₂₁ has one of the formulas:



wherein:

y₁ is 0 or 1;

each y₂ is, independently, 0 to 10;

y₃ is 1 to 10;

E is N(R₄₁)(R₄₂) or N=C(R₄₁)(R₄₂);

each R₄₁ and each R₄₂ is independently H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₄₁ and R₄₂ taken together form a nitrogen protecting group; or R₄₁ and R₄₂ taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

DOCKET NO.: ISIS-4803
Application No.: 09/973,981
Office Action Dated: February 4, 2004

PATENT

B is a nucleobase;

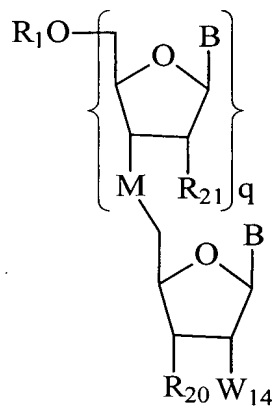
M is an optionally protected internucleoside linkage;

q is 0 to about 50; and

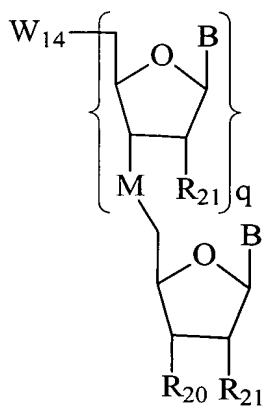
v is from zero to about 10;

provided that when said compound has formula XVIC, at least one R_{21} is a group other than hydrogen, and when said compound has formula XVIC or XVID, q is at least 1.

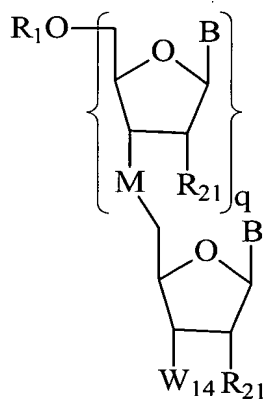
114 (Previously Presented) A compound having formula XVIA, XVIB, XVIC or XVID:



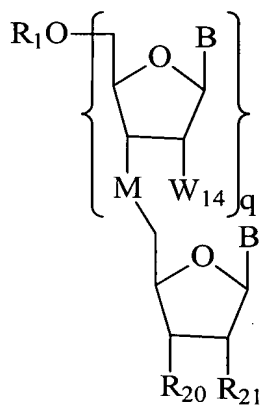
XVIA



XVIC



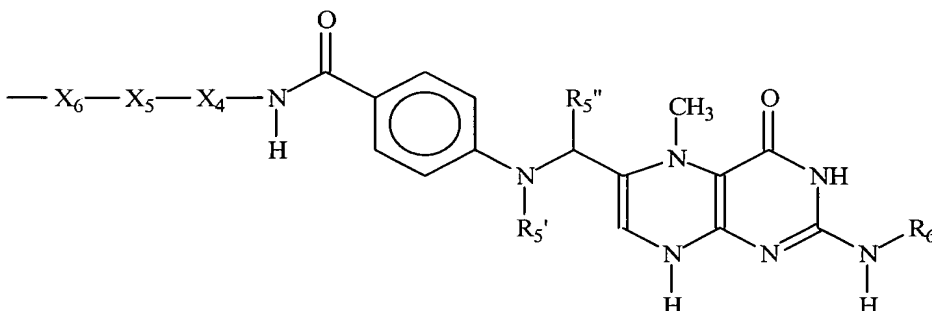
XVIB



XVID

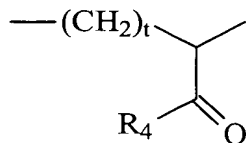
wherein:

W_{14} has the formula:



wherein:

X_4 is $-CH(X_{4'})$ or a group of formula:



$X_{4'}$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

X_5 is $-N(X_6)C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$, $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$, $-C(O)(CH_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6 and X_6' is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl, C_6 - C_{14} aralkyl, C_3 - C_{14} cycloalkyl, C_5 - C_{14} fused cycloalkyl, C_4 - C_{14} heterocycle, C_4 - C_{14} heterocyclylalkyl, C_4 - C_{14} heteroaryl and C_4 - C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen and X_6' is not a bond;

R_1 is hydrogen or a hydroxyl protecting group;

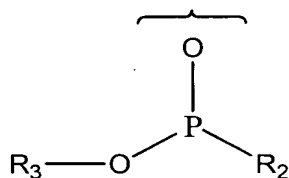
R_4 is a hydroxyl group or a protected hydroxyl group;

each R_5 and R_{40} is, independently, hydrogen, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl or an amino-protecting group

R_{50} is hydrogen, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl, C_6 - C_{14} aralkyl, C_3 - C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

R_6 is hydrogen or an amino protecting group;

R_{20} is hydroxyl or a group of formula:



R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

R_3 is a phosphorus protecting group;

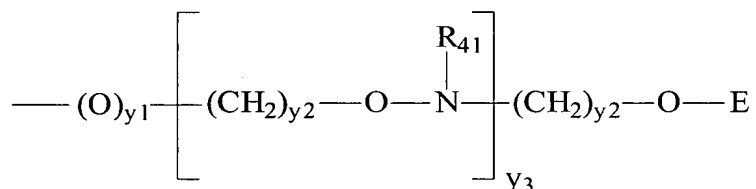
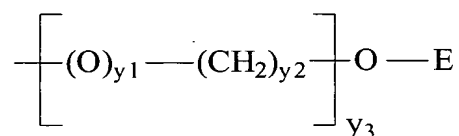
R_{21} is hydrogen, hydroxyl, fluoro or a group of formula $Z-R_{22}-(R_{23})_v$;

Z is O, S, NH or $N-R_{22}-(R_{23})_v$;

R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether;

or R_{21} has one of the formulas:



wherein:

$y1$ is 0 or 1;

each $y2$ is, independently, 0 to 10;

$y3$ is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

DOCKET NO.: ISIS-4803
Application No.: 09/973,981
Office Action Dated: February 4, 2004

PATENT

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

B is a nucleobase;

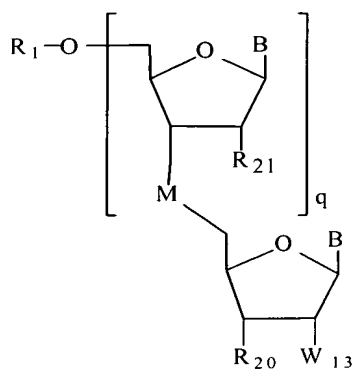
M is an optionally protected internucleoside linkage;

q is 0 to about 50; and

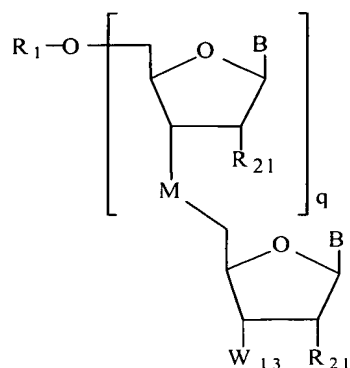
v is from zero to about 10;

provided that when said compound has formula XVID, q is at least 1.

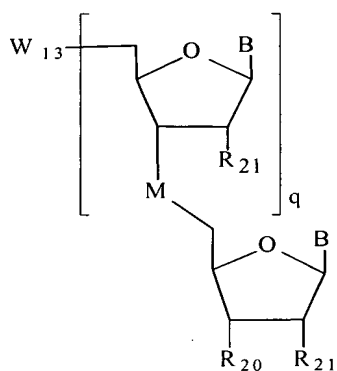
115 (Previously Presented) A compound having the formula XIII A, XIII B, XIII C or XIID:



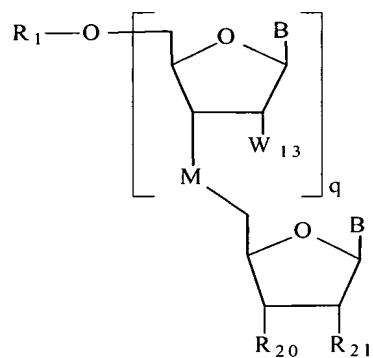
XIII A



XIII B



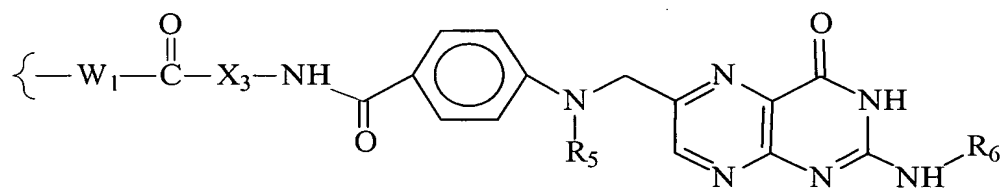
XIII C



XIID

wherein:

W_{13} has the formula:



R_1 is H or a hydroxyl protecting group;

B is a nucleobase;

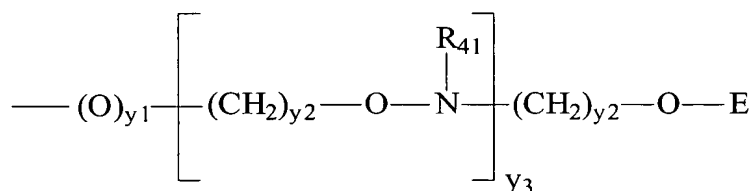
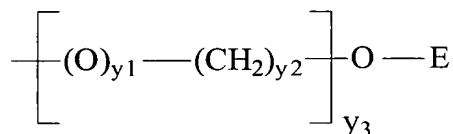
each R_{21} is H, OH, F, or a group of formula $Z-R_{22}-(R_{23})_v$;

Z is O, S, NH or $N-R_{22}-(R_{23})_v$;

R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether;

or R_{21} has one of the formulas:



wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is N(R₄₁)(R₄₂) or N=C(R₄₁)(R₄₂);

each R₄₁ and each R₄₂ is independently H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₄₁ and R₄₂ taken together form a nitrogen protecting group; or R₄₁ and R₄₂ taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

v is from 0 to about 10;

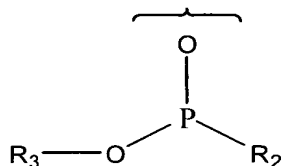
q is 0 to about 50; and

v is from zero to about 10;

M is an optionally protected internucleoside linkage;

W₁ is a linking group, O, NH or S;

R₂₀ is hydroxyl or a group of Formula:



R₂ is -N(R₇)₂, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

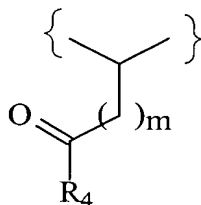
R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

R₅ is H or an amino protecting group;

R_6 is H or an amino protecting group;

X_3 has the formula XII:



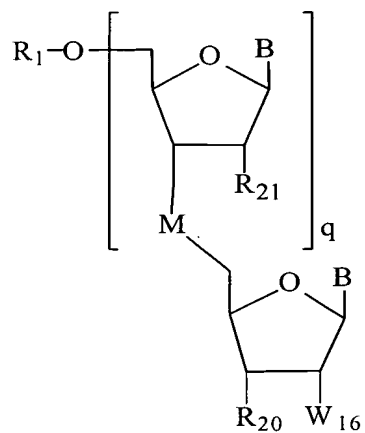
XII

wherein m is 1 or 2; and

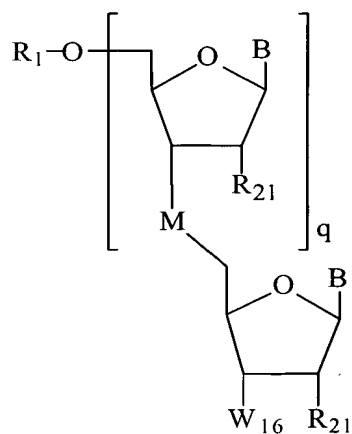
R_4 is a hydroxyl group, or a protected hydroxyl group;

provided that when said compound has formula XIIC, at least one R_{21} is a group other than hydrogen, and when said compound has formula XIIC or XIID, q is at least 1.

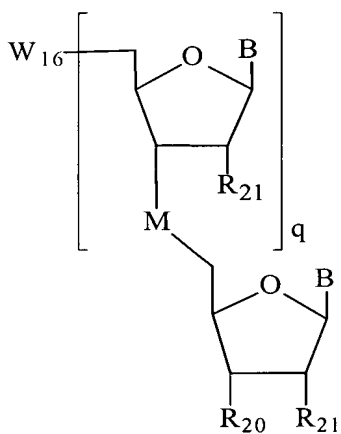
116 (Previously Presented) A compound having the formula XVIA, XVIB, XVIC or XVID:



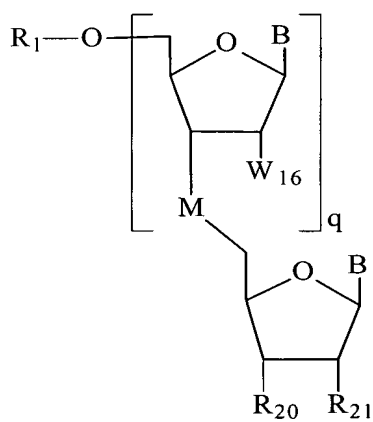
XVIA



XVIB



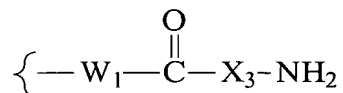
XVIC



XVID

wherein:

W₁₆ has the formula:



R₁ is H or a hydroxyl protecting group;

B is a nucleobase;

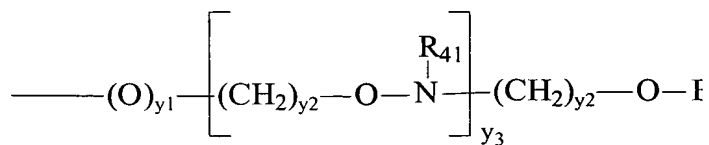
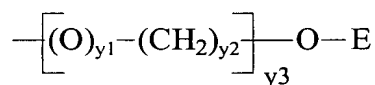
each R₂₁ is H, OH, F, or a group of formula Z-R₂₂-(R₂₃)_v;

Z is O, S, NH or N-R₂₂-(R₂₃)_v;

R₂₂ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₁-C₂₀ akoxy, C₂-C₂₀ alkenyloxy, or C₂-C₂₀ alkynyloxy;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether;

or R₂₁ has one of the formulas:



wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

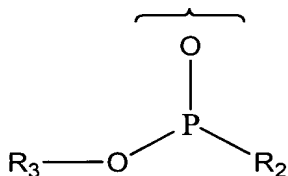
v is from 0 to about 10;

q is 0 to about 50;

M is an optionally protected internucleoside linkage;

W_1 is a linking group;

R_{20} is hydroxyl or a group of Formula:



R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

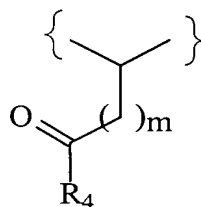
R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

R_3 is a phosphorus protecting group;

X_3 has the formula XII:

DOCKET NO.: ISIS-4803
Application No.: 09/973,981
Office Action Dated: February 4, 2004

PATENT

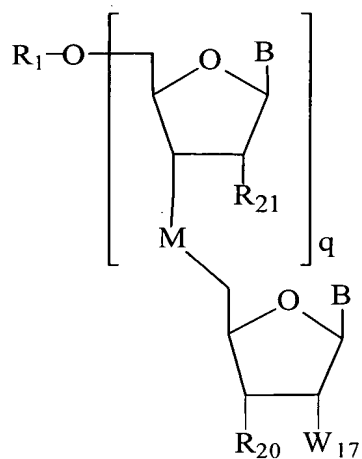


XII

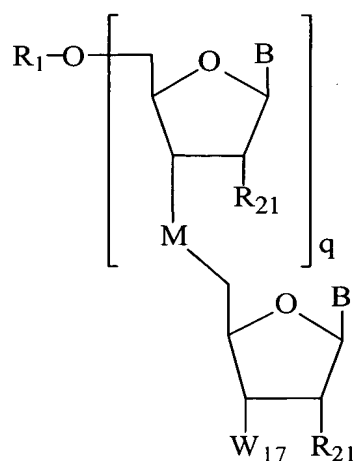
wherein m is 1 or 2;

R₄ is a hydroxyl group, or a protected hydroxyl group; and
provided that when said compound has formula XVII, q is at least 1.

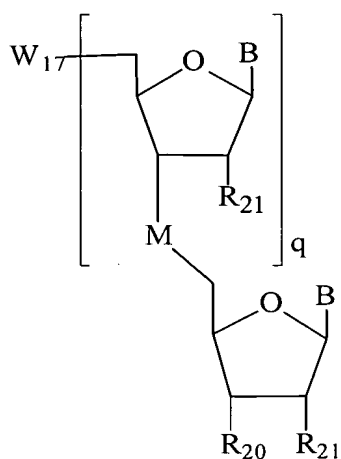
117 (Previously Presented) A compound having the formula XVIIA, XVIIIB, XVIIIC or XVIIID:



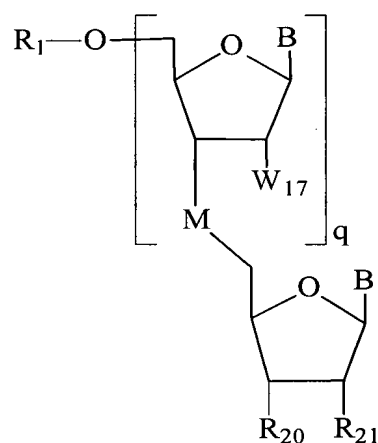
XVIIA



XVIIIB



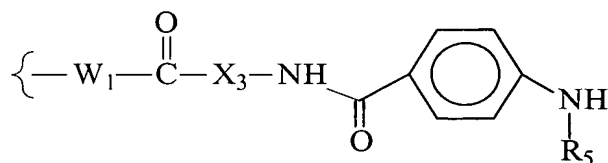
XVIIIC



XVIIID

wherein:

W_{17} has the formula:



R_1 is H or a hydroxyl protecting group;

B is a nucleobase;

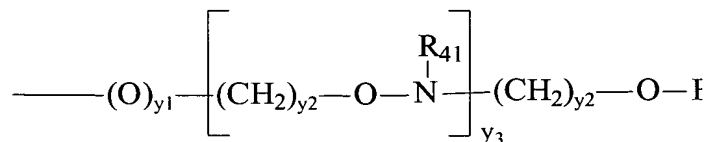
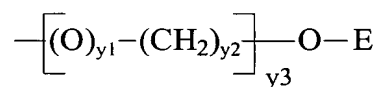
each R_{21} is H, OH, F, or a group of formula $Z-R_{22}-(R_{23})_v$;

Z is O, S, NH or $N-R_{22}-(R_{23})_v$;

R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether;

or R_{21} has one of the formulas:



wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is N(R₄₁)(R₄₂) or N=C(R₄₁)(R₄₂);

each R₄₁ and each R₄₂ is independently H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₄₁ and R₄₂ taken together form a nitrogen protecting group; or R₄₁ and R₄₂ taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

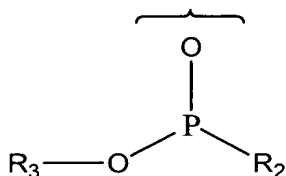
v is from 0 to about 10;

q is 0 to about 50;

M is an optionally protected internucleoside linkage;

W₁ is a linking group, O, NH or S;

R₂₀ is hydroxyl or a group of Formula:



R₂ is -N(R₇)₂, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

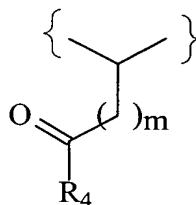
R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

X₃ has the formula XII:

DOCKET NO.: ISIS-4803
Application No.: 09/973,981
Office Action Dated: February 4, 2004

PATENT



XII

wherein m is 1 or 2;

R₄ is a hydroxyl group, or a protected hydroxyl group; and

R₅ is H or an amino protecting group;

provided that when said compound has formula XVIII, q is at least 1.